Kidney International, Vol. 63, Supplement 85 (2003), pp. S88–S90

Usefulness of pamidronate in severe secondary hyperparathyroidism in patients undergoing hemodialysis

JOSE-VICENTE TORREGROSA, AGUSTIN MORENO, MERÇE MAS, JOAN YBARRA, and DAVID FUSTER

Renal Transplant Unit and Nuclear Medicine Department, Hospital Clinic, Institut Medic Barcelona, University of Barcelona, Barcelona, Spain

Usefulness of pamidronate in severe secondary hyperparathyroidism in patients undergoing hemodialysis.

Background. Although bisphosphonates have been widely used to treat bone diseases characterized by increased bone resorption, there are limited data showing their possible usefulness in patients on hemodialysis (HD) with secondary hyperparathyroidism.

Methods. The aim of this study was to evaluate the efficacy and safety of pamidronate in HD patients affected by severe secondary hyperparathyroidism and moderate hypercalcemia who were receiving intravenous calcitriol (Calcijex®).

Results. In this prospective one-year, open-labeled study, 13 patients (9 women/4 men) with a mean age of 64 ± 9 years and a mean time on dialysis of 94 ± 61 months were evaluated. The inclusion criteria were: iPTH >500 pg/mL, Ca >11 mg/dL, P <6 mg/dL, and osteopenia (T-score <−1 SD). Blood levels of Ca, P, alkaline phosphatase (AP), and iPTH were assessed at the beginning of the study and every month. Radiographs of the vertebral spine and bone mineral density (BMD) (lumbar spine and femoral neck) were assessed basal and every 6 months. All patients received 60 mg of pamidronate intravenously every two months throughout the study period. Calcitriol and phosphate binders were adjusted according to iPTH, Ca, and P blood levels. BMD increased in both the lumbar and femoral neck scans (mean increase of 33%) at 6 and 12 months. iPTH increased at 3 months in all patients, and decreased more than 50% in 10 patients after increasing the calcitriol doses. Three patients had no response. A slight decrease in Ca and P was observed in all patients with no significant changes in AP. There were no adverse events.

Conclusion. Pamidronate is effective in controlling hypercalcemia in patients on HD with secondary hyperparathyroidism and allows for a more aggressive use of intravenous calcitriol.

Bisphosphonates are potent antiresorptive agents used to treat a variety of bone diseases that are characterized by increased bone resorption, including malignancy-associated hypercalcemia [1].

Patients affected by renal insufficiency on hemodialysis are at increased risk for developing secondary hyperparathyroidism and hypercalcemia. Although SHP can be controlled medically in most patients, if hypercalcemia is present, medical management may be very difficult, and parathyroidectomy could be the unique alternative.

On the other hand, the demographics of these patients have progressively changed, with an increasing proportion of elderly persons with the associated higher risk of osteoporosis, being included in dialysis therapy. Certainly, hypercalcemia of osseous origin and osteoporosis could be present in patients on hemodialysis affected by secondary hyperparathyroidism. Bisphosphonates, then, could be useful in managing serum calcium and preventing bone loss in these patients.

Pamidronate is a bisphosphonate that has been studied and shown to be well tolerated and beneficial in the treatment of hypercalcemia [2], osteoporosis, steroid-induced osteoporosis, and primary hyperparathyroidism [3]. The parenteral form of pamidronate has shown to be well tolerated in doses up to 90 mg/day in adults [2].

However, limited data on pamidronate's effects in dialysis patients are available at present.

The aim of this study was to evaluate the efficacy and safety of pamidronate in patients on HD affected by severe secondary hyperparathyroidism and moderate hypercalcemia receiving several doses of intravenous calcitriol.

METHODS

In this prospective one-year, open-labeled study, thirteen patients (9 females and 4 males) on hemodialysis, with a mean age of 64 ± 9 years (range, 54 to 78), and a mean time on dialysis of 94 ± 61 months, were enrolled. Primary renal diseases included polycystic kidney disease in 4 cases; chronic pyelonephritis in 3 cases; chronic glomerulonephritis in 3 cases; nephroangioesclerosis in 1 case; and in 2 cases, the disease was unknown. Four patients had previously experienced a renal graft rejection and were returned to hemodialysis.

Inclusion criteria were the following: presence of a

Key words: bisphosphonates, calcitriol, osteoporosis.

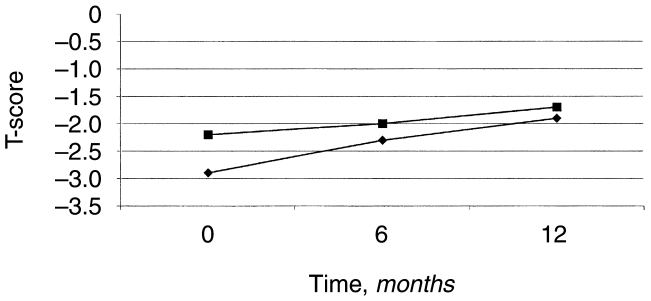

Fig. 1. Bone mineral density evolution expressed as T-score.

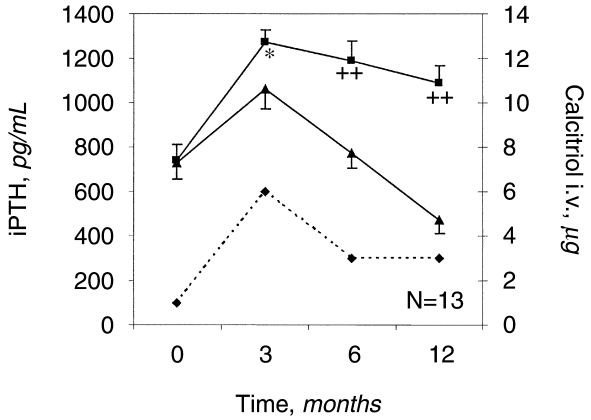

Fig. 2. iPTH evolution (responders and non-responders) and calcitriol dose throughout the study period.

persistent severe secondary hyperparathyroidism (defined as a serum iPTH higher of 500 pg/mL), in addition to a serum calcium level >11 mg/dL and serum phosphorus level <6.5 mg/dL, and osteopenia (T-score <1 SD). No patients had undergone parathyroidectomy, and patients diagnosed of diabetes mellitus were excluded. The study was conducted according to good clinical trial practice and the principles of the Declaration of Helsinki. All patients gave their informed consent to the study.

All patients received pamidronate every two months throughout the study period. Pamidronate was given intravenously in dose of 60 mg during the hemodialysis session. Intravenous calcitriol (Calcijex®) and phosphate binders were administered according to the measured iPTH, Ca, and P blood levels.

Blood levels of calcium, phosphorus, alkaline phosphatase, and iPTH were assessed at the beginning of the study and every month for one year. Radiographs of the vertebral spine and bone mineral density (lumbar spine and femoral neck) were assessed basal and every six months.

During the study period the patients followed a dialysis schedule of four hours per session three times a week with no changes in the dialysate Ca concentration (1.5 mmol/L). iPTH was measured by an intact-PTH immunoradiometric assay (IRMA; Nichols Institute Diagnostics, San Diego, CA, USA), with a normal range between 12 and 65 pg/mL. Serum Ca, P, and alkaline phosphatases were measured using standard methodology. Bone mineral density was measured with a dual energy x-ray absorptiometer (Lunar DPX-L, Lunar Radiation Corp., Madison, WI, USA). Scans were made of four lumbar vertebrae (L1 to L4) and the right proximal femur. The results were expressed as g/cm^2 and derived by dividing the bone mineral content of hydroxyapatite of each region by the projected bone area.

Data were analyzed using the SPSS 10.0 statistical package (SPSS, Inc., Chicago, IL, USA). Quantitative variables are expressed as mean and standard error of the mean. Analysis of variance (ANOVA) was used to assess the differences between variables. $P < 0.05$ was considered statistically significant.

RESULTS

All patients completed the study. Bone mineral density changes are shown in Figure 1. As is seen, both areas (lumbar spine and femoral neck) were significantly improved at the end of the study period (mean increase of 33%) ($P < 0.01$).

Figure 2 illustrates the kinetics of serum iPTH and calcitriol dose during the study period. Ten out of 13 patients (77%) showed a significant decrease in their serum iPTH and were termed the "PTH-responder group," while the remaining three were termed the "PTH non-responder group." A peak iPTH value was noticed in all patients at three months of pamidronate therapy; nevertheless, in the responder group, with the increasing of calcitriol dose, the iPTH value was completely reversed at six months, while at the end of the study, iPTH values were significantly decreased (460 ± 75 pg/mL) ($P < 0.001$). Patients in the "non-responder group" disclosed no significant changes in their iPTH serum levels (P = NS), despite the increased calcitriol dose.

The mean calcitriol dose was 1 μg/week at the beginning of the study, 6 μg/week at three months, and 3 μg/week from 6 months to the end of the study.

A slight drop in serum calcium and phosphorus levels was detected in both groups simultaneously (Fig. 3), with no significant changes in alkaline phosphatase.

There were no adverse events during or after the pamidronate infusion. No fractures were observed during the study period, assessed by radiographs of the vertebral spine.

DISCUSSION

The present study shows that pamidronate is capable of controlling hypercalcemia and osteopenia secondary to high bone turnover hyperparathyroidism in patients on HD, providing a better optimization of calcitriol management in these patients.

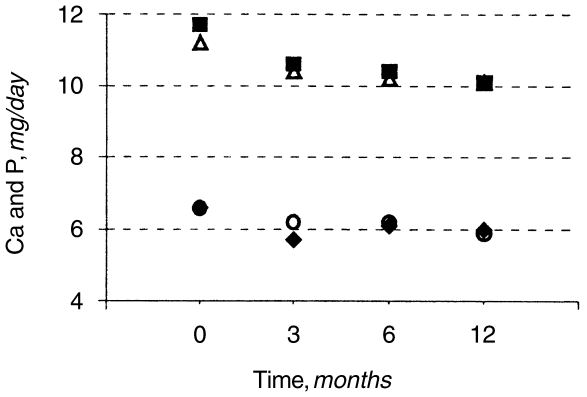

Fig. 3. Ca and P blood levels throughout the study period. R is the PTH responder group and Non-R is the PTH non-responder group.

The combination of high bone turnover hyperparathyroidism and the therapy with pamidronate had a rapid effect on the amelioration of bone mineral density.

Bisphosphonates are stable pyrophosphate analogs that act mainly by promoting osteoclast apoptosis, and therefore, decreasing bone resorption and subsequent bone remodeling. Their efficiency is well established in patients without renal insufficiency with respect to increasing bone mineral density, decreasing new fracture rates, and in the prevention of corticoid-induced osteoporosis.

There are few studies on the use of bisphosphonates in patients with end-stage renal disease [4–11], and only three of them are using pamidronate [8, 10, 11]. Because of the renal elimination and prolonged skeletal retention of bisphosphonates, their administration in uremic patients has been of concern, and they have generally been used only to treat hypercalcemic episodes. However, it would be reasonable to use them in dialysis patients to treat high bone turnover hyperparathyroidism because bisphosphonates inhibit PTH-mediated bone resorption [7]. On the other hand, a combination of bisphosphonates and calcitriol would be reasonable, too, since the development of hypercalcemia often prevents adequate calcitriol therapy [7].

Patients on HD are at increased risk for developing high bone turnover hyperparathyroidism. In these patients, the early and rapid suppression of bone resorption, promoted by high doses of potent bisphosphonates, with the yet unchanged bone formation rate may decrease serum calcium concentrations with a compensatory increase in PTH secretion, as was seen in our study.

The increased dose of calcitriol permitted control of this increase in iPTH secretion and was able to posteriorly normalize it with a non-hypercalcemic effect.

CONCLUSION

Bisphosphonates represent potentially useful tools in dialysis patients with severe secondary hyperparathyroidism. Therapy with intravenous pamidronate is effective in controlling hypercalcemia and allows a more aggressive use of calcitriol, while at the same time dramatically improves the bone mineral density.

In patients on HD, further studies are needed to determine the best bisphosphonates, the optimal dose, the frequency of administration, and when to stop them in order to prevent bone loss and to obtain a better control of secondary hyperparathyroidism. This will enlarge the therapeutic window for administration of vitamin D derivatives.

Reprint requests to Jose-Vicente Torregrosa, Renal Transplant Unit, Hospital Clinic, C/ Villarroel, 170, 08036 Barcelona, Spain.
E-mail: vtorre@clinic.ub.es

REFERENCES

1. Papapoulos SE: Bisphosphonates, in *The Aging Skeleton*, edited by Rossen CJ, Glowaky J, Bilezikian JP, San Diego, Academic Press, 1999, pp 541–549
2. Fitton A, McTavish D: Pamidronate: A review of its pharmacological properties and therapeutic efficacy in resorptive bone disease. *Drugs* 41:289–318, 1991
3. Schmidli R, Wilson I, Espiner E, *et al*: Aminopropylidine diphosphonate (APD) in mild primary hyperparathyroidism: Effect on clinical status. *Clin Endocrinol* 32:293–300, 1990
4. Hamdy NAT, McCloskey EV, Brown CB, *et al*: Effects of clodronate in severe hyperparathyroid bone disease in chronic renal failure. *Nephron* 56:6–12, 1990
5. Yap AS, Hockings GI, Fleming SJ, *et al*: Use of aminohydroxyproline bisphosphonate (AHPrBP) for the treatment of hypercalcemia in patients with renal impairment. *Clin Nephrol* 34:225–229, 1900
6. Hené RJ, Visser WJ, Duursma JA, *et al*: No effect of APD (aminohydroxypropylidene bisphosphonate) on hypercalcemia in patients with renal osteodystrophy. *Bone* 11:15–20, 1990
7. Malluche HH: The possible use of bisphosphonates in the treatment of renal osteodystrophy. *Clin Nephrol* 38:S87–S91, 1992
8. Davenport A, Goel S, Mackencie J: Treatment of hypercalcemia with pamidronate in patients with end stage renal failure. *Scan J Urol Nephrol* 27:447–451, 1993
9. Ring T, Sodemann B, Nielsen C, *et al*: Mineralization defect but no effect on hypercalcemia during clodronate treatment in secondary hyperparathyroidism. *Clin Nephrol* 44:209–210, 1995
10. Machado C, Flombaum C: Safety of pamidronate in patients with renal failure and hypercalcemia. *Clin Nephrol* 45:175–179, 1996
11. Sellers E, Sharma A, Rodd C: The use of pamidronate in three children with renal disease. *Pediatr Nephrol* 12:778–781, 1998